Congressional Justification

National Institute of Dental and Craniofacial Research

Authorizing Legislation: Section 301 of the Public Health Service Act, as amended. Reauthorizing legislation will be submitted.

Budget Authority:

FY 2000 Actual		FY 2001 Estimate		FY 2002 Estimate		Increase or Decrease	
FTEs	BA	FTEs	BA	FTEs	BA	FTEs	BA
295	$268,904,000	310	$306,211,000	310	$341,898,000	0	$35,687,000

This document provides justification for the FY 2002 activities of the National Institute of Dental and Craniofacial Research, including HIV/AIDS activities. A more detailed description of NIH-wide Fiscal Year 2002 HIV/AIDS activities can be found in the NIH section entitled "Office of AIDS Research (OAR)."

Introduction

"The intent of this first-ever Surgeon General's report on oral health is to alert Americans to the full meaning of oral health and its importance in relation to general health and well-being." Thus begins Oral Health of America: A Report of the Surgeon General, a report released this past spring.[1] This report, which was led by staff from the National Institute of Dental and Craniofacial Research (NIDCR), critically evaluates the science base and highlights the breadth of conditions that affect the oral, dental, and craniofacial tissues. The major message of the report is that oral health is integral and essential to the general health and well being of all Americans. Moreover, the report emphasizes that although our population's oral health has benefited from major accomplishments in disease prevention and health promotion, many individuals still experience needless pain and suffering due to untreated diseases.

The Institute is uniquely positioned to eliminate oral health disparities and improve quality of life. New knowledge is needed to understand the complex diseases affecting the mouth and face. Further investigation is needed to understand the nature and extent of associations between oral infections and systemic conditions such as diabetes, cardiovascular disease, low-birth weight and respiratory infections. Studies targeted toward understanding and addressing disparities that

[1] U.S. Department of Health and Human Services, *Oral Health in America: A Report of the Surgeon General.* Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000.

exist due to race/ethnicity, socioeconomic status, gender, age, and disability are required. Ultimately investigations need to focus on ways to promote health, not just prevent disease.

The past investment in science has resulted in oral and dental disease prevention advances that have been estimated to generate savings of $5 billion a year in dental expenditures.[2] This yearly savings is more than the cumulative budget of the NIDCR since its inception in 1948. Future advances, however, will come at the interfaces of traditional scientific disciplines. Additional collaborations among health care sectors will also be needed to ensure timely translation of basic science findings into improvement of health.

The Institute is ready to address these challenges through support of science, continued development of the nation's research capacity and by working with all organizations and groups to promote oral health. NIDCR's strategic plan, Shaping the Future (www.nidcr.nih.gov) identifies six areas of science that provide the framework for our research portfolio:

1. Biomimetics and Tissue Engineering;
2. Oral Infections and Immunity;
3. Oral and Pharyngeal Cancers;
4. Chronic and Disabling Diseases;
5. Craniofacial Anomalies and Injuries; and
6. Behavior, Health Promotion and Environment.

The Institute is a co-lead with other agencies for the oral health promotion and disease prevention objectives of Healthy People 2010, and as such partners with voluntary and professional groups, industry, academia, and other government agencies. In addition, the Institute is taking the lead in accelerating the science base and the effective application of science to improve oral health, one of the major components of the National Oral Health Plan called for by the Surgeon General.

Reducing Oral Health Disparities

The Challenge:

As we move into the 21st century, NIDCR can look back to over 50 years of progress in understanding, treating, and preventing the complex diseases that affect the mouth and face. However, not all Americans have shared equally in the benefits of these important scientific breakthroughs. Disparities in oral health continue to exist at all ages and among the different population groups that comprise our society. For example:

- Oral and pharyngeal cancers are diagnosed in about 30,000 Americans annually; 8,000 die from these diseases each year. This disease disproportionately affects older Americans, men and African Americans. For example, African American men are one-third more likely to be diagnosed with oral cancer than whites, and their 5-year survival rate is only 28 percent, compared to a 53 percent survival rate for white men.

[2] Centers for Disease Control and Prevention (CDC), "Fluoridation of Drinking Water to Prevent Dental Caries", *Morbidity and Mortality Weekly Report 1999*, 48: 933-940.

- Dental caries is the most common chronic childhood disease–5 times more common than asthma and 7 times more common than hay fever. Minority children have more dental decay than white children do.
- Cleft lip/palate, one of the most common birth defects, is estimated to affect 1 out of 600 live births for whites and 1 out of 1,850 live births for African Americans.

Reducing these and other health disparities is a continuing priority for NIDCR as it is for the National Institutes of Health (NIH) as a whole.

Progress:

The causes of oral health disparities are not fully understood; genetic, environmental, and behavioral factors are all likely to play a role. We are just beginning to unravel the complexity of a person's susceptibility to oral disease and beginning to identify the many factors that contribute to disease progression and response to treatment. Potential associations between oral diseases and general health conditions require further investigation of the basic mechanisms that may contribute to these relationships. Our Strategic Plan to Reduce Racial and Ethnic Disparities(http://www.nidcr.nih.gov/opportunities/healthdisp/Health_Disparities_StrategicPlan.pdf) includes three complementary elements: 1) cross-cutting science activities; 2) enhancement of research capacity; and 3) communication of research findings to the public and health care providers.

Current cross-cutting science activities to address health disparities

Oral infectious disease

Dental caries and periodontal diseases are the most prevalent infections of humans and affect individuals throughout their life span. The pathogenic mechanisms that underlie these infections involve a complex interplay of bacterial biofilms, diet/nutrition and host defense. The disease profile, progression and prognosis vary with age and other factors yet to be identified. The distribution of the severity of the disease presents a challenge. For example, although about 78 percent of 17 year olds have experienced caries, approximately 80 percent of tooth decay in permanent teeth is now found in only 25 percent of school-age children—often children from minority groups.[3] Research supported by the NIDCR addresses the treatment and prevention of dental caries not only as a way of directly reducing the incidence and prevalence within socioeconomic status and ethnically/racially distinct groups, but also as a means of stopping or preventing, respectively, the sequelae of the disease. This year NIDCR will host an NIH consensus development conference on the management of caries.

The proposed linkages between periodontal diseases and general health conditions are being investigated as well. The relationships may include a combination of microbial factors and host inflammatory cytokines that have potent effects on the systemic tissues. NIDCR currently supports basic research and pilot intervention studies to more fully characterize the association between periodontitis and conditions such as atherosclerosis, stroke, respiratory diseases and diabetes.

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[3] National Center for Health Statistics (NCHS). Third National Health and Nutrition Examination Survey (NHANES III) reference manuals and reports. Hyattsville, MD: NCHS, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1996.

Oral and Pharyngeal Cancer

Detection of oral and pharyngeal cancers often occurs late in disease progression, and this limits treatment options and survival. Efforts are being made to detect the disease at its earliest stages using biomarkers found in blood, saliva or oral fluids. A recent research advance identifying genetic risk factors could improve screening protocols for African Americans, who are at greater risk of developing oral and pharyngeal cancers. These cancers are linked to tobacco- and alcohol-related diseases. To begin to explain the differences in survival rates between whites and African Americans, investigators have been studying genetic differences in smokers with and without (primary) oral cancer. They identified polymorphisms in genes that code for enzymes involved in the metabolic detoxification of tobacco carcinogens termed glutathione S-transferases (GSTs). A strong association was found between the absence of one form of GST in African Americans with oral cancer and heavy tobacco use. However, no significant associations were observed between these genotypes and oral cancer risk in whites. Thus, the results indicate that these genotypes play important roles in risk for oral cancer among African Americans and implicate these enzymes as important tobacco carcinogen detoxifying enzymes in this population. Consequently, these genetic polymorphisms may be used in the future to screen and identify those African Americans at highest risk of oral cancers.

Enhancement of Research Capacity to Redress Oral Health Disparities

NIDCR is enhancing its research capacity by instituting training and career development programs that encourage individuals from racial and ethnic minorities to enter and remain in science careers. New training mechanisms that will be initiated in FY 2001 have been designed to encourage multi-disciplinary training that goes beyond traditional disciplines.

We are also taking steps to ensure appropriate representation of all populations in clinical trials. In part, this is being accomplished by providing investigators with the tools to facilitate community-based linkages for research.

Communication of Research Findings to Redress Oral Health Disparities

We are expanding efforts to communicate research findings appropriately to populations at highest risk and to health professionals. For example, the Institute has embarked upon planning grants for statewide models aimed at preventing oral cancer. Preliminary findings have shown that public and health professionals' knowledge of risk factors and preventive practices require reinforcement, and community-based strategies are needed. In addition, one of NIDCR's Comprehensive Oral Health Research Centers of Discovery, devoted to oral cancer, will be initiating an education and community outreach core. A part of the program is directed toward populations at risk, particularly African Americans.

Activities for FY 2002:

In FY 2001, NIDCR established the Centers for Research to Reduce Oral Disparities in partnership with the Health Resources and Services Administration (HRSA), the Centers for Disease Control and Prevention (CDC), as well as numerous NIH institutes and offices. These centers will remain a major focus for NIDCR in FY 2002; funding for these centers will continue in support of a broad base of research on health disparities—ranging from fundamental studies of genetic differences in disease susceptibility to clinical studies and trials leading to the design and evaluation of interventions to treat and prevent disease.

Specialized Programs of Research Excellence

In FY 2002, NIDCR and the National Cancer Institute (NCI) will introduce a new research initiative to co-fund Specialized Programs of Research Excellence (SPOREs) on head and neck cancers. These specialized programs are designed to support translational research that will have the most immediate impact on reducing the incidence, morbidity and mortality of organ-site cancers. Basic and clinical researchers will work together to search for new approaches to early detection, diagnosis, treatment, and prevention of cancers. These programs are not only expected to conduct a wide spectrum of research, but also to contribute to the development of research model systems and the expansion of the research base through collaborations with laboratory scientists and clinicians nationwide.

Replacing and Restoring Damaged Tissues and Organs

The Challenge:

As Americans continue to live longer, there is an increased demand for better ways to manage the challenges brought on by inherited disorders, infectious and neoplastic diseases, craniofacial-oral-dental trauma, and the many other chronic and disabling diseases and disorders that affect the body. The demand for new materials and reparative procedures is staggering both in scope and cost. Each year, millions of Americans suffer some type of tissue loss or end-stage organ failure. The total cost for these patients exceeds $400 billion per year[4]. Included in these annual figures are roughly 20,000 organ transplants, 500,000 joint replacements, and literally millions of dental-oral-craniofacial procedures, ranging from tooth restorations to major reconstruction of facial hard and soft tissues.

Biomimetics (literally to mimic biology) and tissue engineering are new disciplines where the life and physical sciences meet. This interdisciplinary field takes clues from nature to develop novel approaches to repair and replace tissues of the body. For example, the refrain, "scarcer than hen's teeth" is no longer accurate – through dissection of the natural events that guide the development of teeth, investigators have been able to grow teeth in chicks.

Progress:

4Langer, R. and Vacanti, J. P. "Tissue Engineering", *Science*, May 14, 1993, 260,. 920-925.

Improved Dental and Orthopedic Implants

NIDCR–supported investigators have developed ways to improve titanium-based implants using "bioactive" nanoparticle coatings on the surface of the device. This coating facilitates bonding between the implant and the adjoining bone by providing an interface that is more favorable to bone-forming cells. That is, bones forming cells sense "foreign" objects such as implants and thus fail to incorporate the objects within the bone with the same efficiency. By coating the implant interface with a biocompatible surface, the bone cell's response is tipped toward building bone around the device.

How Cells Engineer Connective Tissue Matrix

Fibronectin is an essential (protein) component of connective tissue. It is involved in normal embryonic development and wound healing, the development of fibrosis (excess connective tissue) and scar tissue, and the spread of some forms of cancer. NIDCR researchers have learned the secrets of how cells stretch fibronectin on their outer surfaces to become organized into a three-dimensional matrix. Investigations have shown that several different drugs halt or accelerate this process. Knowing how this lattice-work is created lays the groundwork to control or mimic this process, providing the potential to engineer replacement tissues and to develop new strategies to stop the spread of cancer at the molecular level.

Activities for FY 2002:

Applying Biomimetics to Orofacial Tissue Restoration

NIDCR scientists are using the principles of biomimetics to create replacement bone, cartilage, and tooth structures. Scientists today can mimic biological systems to fabricate high-performance mineral-polymer composites that in the near future will be placed directly into a patient's mouth to replace or repair structures such as bone and teeth. Investigators are also looking at how biomimetically derived materials can be used for drug and gene delivery in the treatment of a variety of diseases of the oral cavity as well as those of the entire body.

Researchers have made considerable progress in using "inductive" molecules to promote the formation of new bone, which would be particularly useful for regeneration of the bone supporting teeth. Investigators also are studying ways to induce the blood vessel formation needed to metabolically support tissue and integrate it with the body. In other NIDCR-sponsored research, scientists are combining the use of inductive molecules and cell transplantation to grow large masses of tissue in relatively short periods of time. These exciting advances are moving scientists forward in their goal to develop tissue replacement technologies that perform ideally in the human biological environment. NIDCR plans to expand its efforts in this area by facilitating opportunities for creating new biological-in-origin (biomimetically derived) materials and composites of biological and non-biological materials for the restoration of oral, dental and craniofacial structures.

Construction of an Artificial Salivary Gland

Using the new techniques and principles of tissue engineering, NIDCR scientists are working on development of a "first of its kind" artificial salivary gland that offers hope for these patients with severely damaged salivary glands. Saliva is a remarkable, multipurpose fluid whose presence most of us take for granted. Yet each year, 40,000 people suffer a loss of salivary gland function as a result of radiation treatment for head and neck cancer. Although the treatment may be lifesaving, it can permanently damage salivary glands located in the field of radiation. In addition, it is estimated that more than one million Americans (primarily women) are afflicted with Sjögren's syndrome, an autoimmune disease whose symptoms include dry mouth and dry eyes. Whether salivary glands are irreparably damaged by a disease such as Sjögren's syndrome, or by treatment such as radiation for head and neck cancer, the resulting loss of saliva flow markedly impairs quality of life. Without adequate saliva, patients may experience difficulty speaking, chewing and swallowing. They may also experience rampant tooth decay, mucosal infections such as candidiasis, loss of taste, and considerable oral discomfort. No effective treatments currently exist to help these patients.

Initial efforts are focused on creating a small tube that can be placed into the cheek (buccal mucosa) of patients whose salivary gland cells have been destroyed. The tube, which is made of a biodegradable matrix, would be coated with a purified extracellular matrix protein, and lined cells engineered to secrete a saliva-like substance. Investigators are also looking at how salivary glands can be used as bioreactor materials to deliver drug or hormones in the treatment of a variety of systemic diseases. Scientists believe that the artificial salivary gland will be ready for clinical testing within 5-7 years.

Development of Biomedical Computing Tools to Support Orofacial Research

Increasingly, biology is moving from "bench"-based science to one in which computer technologies routinely complement and at times even replace work performed in the laboratory. Enormous stores of different types of information are being generated, including DNA sequences as genomes are being solved; clinical images that capture often subtle phenotypic differences among patients, and clinical laboratory tests from thousands of patients enrolled in clinical trials. Software tools are required to integrate these disparate types of information into single databases that can be interrogated in real time by clinicians and investigators. Careful consideration must also be given to ensuring appropriate patient confidentiality in building such complex databases.

NIDCR plans to support development of: tools for data collection and interrogation; models or simulation environments; computer algorithms to facilitate analysis of data stores; and new statistical methodologies to analyze biomedical problems.

Preventing and Treating Craniofacial Disorders

The Challenge:

Cleft lip/palate is one of the most common birth defects. Greater than 1 child in 1000 live births suffers from either cleft lip/palate.[5] Other birth defects—such as hereditary ectodermal dysplasias, where all or most teeth are missing or misshapen—cause lifetime problems that can be devastating to children and adults. By unraveling the genetic basis of craniofacial disorders, investigators seek the means to detect these disorders earlier and hopefully intervene, thereby preventing birth defects.

Progress:

Researchers Identify Relationships Among Congenital Disorders

Hypohidrotic ectodermal dysplasia and immune-deficiency (HED-ID) is a rare but very serious genetic disorder passed from mother to son. Despite intensive treatment, young boys with HED-ID often suffer life-threatening recurrent infections, misshapen or missing teeth, inadequate sweating, and skin disorders. Familia incontinentia pigmenti (IP), a related genetic disorder, causes affected women to miscarry if the fetus is male. Researchers supported by NIDCR recently established a link between these two disorders. Scientists obtained and analyzed DNA samples from four families with children with HED-ID and found genetic mutations in the IKK-gamma protein in each family. More severe mutations in IKK-gamma have been linked to IP. The results move scientists closer to understanding neonatal development of skin, teeth, and hair. In the future, this knowledge may be used to develop new strategies for prevention and treatment of HED-ID, IP, and other genetic disorders.

Identification of Gene for Cleft Lip and Palate/Ectodermal Dysplasia Syndrome (CLPED1)

Advances in genetic studies are shedding light on genes that are important in forming the head and face. The most common of all craniofacial anomalies—and among the most common of all birth defects—are cleft lip with or without cleft palate, and cleft palate alone. Many of the same genes that turn on in the embryo to regulate the movement of cells destined to become the face also control the cells fated to become brain, skin, parts of the heart, the gut, and distant extremities like fingers and toes. NIDCR-sponsored researchers have now identified the gene responsible for one form of cleft lip/palate syndrome, called CLPED1.

CLPED1 includes not only cleft lip and palate, but also ectodermal dysplasia (a congenital defect of the ectodermal tissues that affects the skin, hair, teeth, nails, and sweat glands), developmental defects of the hands, and in some cases, mental retardation. NIDCR-supported investigators have identified the gene responsible for this syndrome as PVRL1, which encodes a protein important in cell-cell adhesion. Mutations in the gene lead to truncated proteins that prevent normal development. The identification of this gene advances our understanding of the processes involved in orofacial development and the mechanisms underlying cleft lip/palate. In turn, this knowledge may be used to develop new approaches to repair and replacement of oral tissues in the future.

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[5] Schulman, J., Edmonds, L.D., McCleran A.B., Jensvold, N., and Shaw, G.M. "Surveillance for and Comparison of Birth Defect Prevalences in two Geographic Areas—United States", 1983-88. *Morbidity and Mortality Weekly Report*, March 19, 1993, 42(1), 1-7.

Activities for FY 2002:

Novel Genes Involved in Craniofacial Disorders

Through a new research initiative, NIDCR is identifying and cataloguing the genes involved in specific stages of craniofacial development to find those responsible for craniofacial disorders and birth defects. Recently, 20,000 different markers from genes active in early embryos were identified. The next goal will be to identify the subset of genes that are expressed uniquely in the developing craniofacial tissues. Information available from the Human Genome Project also is helping to determine the location of expressed genes on human chromosomes. If the expressed genes map to sites close to known human genetic disorders, then they are being tested as a possible cause of that disease.

HIV Oral Transmission and Infection

The Challenge

Oral transmission of HIV has been a focus of epidemiological, animal and basic studies since the early stages of the epidemic. Since HIV can be transmitted via the oral cavity, either through sexual contact or from mother to child, the role of the oral cavity regarding defense and tolerance may be far more significant than previously understood. Data from a recent study showed that 7.8 percent of HIV infections in a study population of homosexual men were due to oral transmission of the virus. More extensive documentation exists regarding the high risk of transmitting HIV from an infected mother to an infant both during delivery as well as through ingestion of infected breast milk. Understanding the basic mechanisms of transmission should lead to better interventions.

Progress

Recent evidence from NIDCR research has indicated that epithelial cell lines of salivary gland origin can be infected in the laboratory with HIV-1. This suggests that epithelial cells in the oral cavity might be targets of HIV-1 and therefore could serve as sources of systemic infections. New emphasis has been directed to the importance of the first cell (s) infected with HIV in the oral cavity. Factors related to transmission from mother to child during delivery and through breast milk also have been the subject of recent research efforts. NIDCR-supported studies of the mucosal factors involved in HIV transmission by breast milk have indicated the importance of the antimicrobial properties of secretory leukocyte protease inhibitor (SLPI), a molecular substance found in mucosal fluids. Results indicated that breast milk collected in the very early post-natal period contained SLPI in transiently high levels that declined within three weeks after delivery, providing a minimally safe period for breast feeding to provide the neonate with an early advantage in nutrition and passive immunization.

Activities for FY 2002

Additional research is needed to better understand both the mechanisms of oral transmission and the role the oral cavity plays in the body's natural defenses against HIV. Through this new research initiative, NIDCR will further develop several key research areas related to the

mechanism of viral entry and the first cell infected, the effect of AZT therapy on oral transmission from mother to child, the relationship between the stage of infection of the "donor" and oral infectivity, and the effect of being concurrently infected with other oral viruses when challenged by HIV. Other topics of investigation include: cell trafficking (controlled movement of cells in and out of tissue) and migration from the peripheral circulation to sites in the oral cavity during inflammation, or co-infection with other organisms; changes that occur in the oral cavity using highly active anti-retroviral therapy (HAART); the oral or salivary molecules that interact with HIV; and the role of molecules known as cytokines that may change the profile of the cellular immune response and that may stimulate otherwise non-immune cells to express co-receptors that are key to viral transmission. The information from these studies, combined with overall investigations of HIV transmission, may help generate new ways to treat AIDS and to prevent the further spread of HIV.

Treating Chronic Diseases and Pain

The Challenge:

It is now appreciated that chronic pain can become a disease in itself, causing long-term detrimental changes in the nervous system. These changes may affect resistance to other diseases as well as effectively destroy quality of life. Pain is a common symptom of craniofacial disorders and may interfere with such vital functions as eating, swallowing and speaking. Twenty-two percent of adults reported some form of oral-facial pain over a 6 month period.[6]

Since the 19th century, oral health researchers have been recognized as leaders in the field of pain management. Their analyses of the cells, pathways, and molecules involved in the transmission and modulation of pain have given rise to a growing variety of medications, often combined with other approaches, that can control acute and chronic pain.

Progress:

Animal Model Shows Pain and Tissue Injury in Newborns Alters Nerve Circuitry and Reaction to Pain Later in Life

Working with an animal model, scientists at the NIDCR have provided the first physical evidence that newborns who experience tissue injury and pain during critical periods of development may undergo a permanent rewiring of their nervous system that increases their sensitivity to pain later in life. Each year, more than 400,000 babies in the United States are born either prematurely or at a low birth weight. Of these, 25,000 are considered to be extremely premature—born at 27 weeks of gestation or less.[7] While 10 or 15 years ago most of these infants did not live, it is no longer unusual for them to survive, thanks to advances in medical technology. However, the medical procedures used to keep them alive and monitor their progress may cause pain and tissue injury. Heel sticks to draw blood, the insertion of IV tubes

[6] Lipton, J.A., Ship, J.A. and Larach-Robinson, D. "Estimated Prevalence and Distribution of Reported Orofacial Pain in the United States", *Journal of the American Dental Association*, October 1993, 124 (10), 115-121.
[7] Institute of Medicine, Committee to Study the Prevention of Low Birth Weight, Division of Health, Promotion and Disease Progression. *Preventing Low Birth Weight.* Washington, D.C.: National Academy Press, 1985.

and nasogastric tubes, and the use of ventilators are some of the modern technologies and procedures that can be both miraculous and painful.

An NIDCR study used newborn rats to explore the effect of tissue injury and pain on the development of pain pathways. An irritant was injected into 1-day-old rats, an age equivalent to 24 weeks gestation in humans. When the animals were examined as adults, it was found that they had an increase in the density of nerve fibers on the left side of the dorsal horn, the layered structure in the spinal cord that propels brain signals up to the brain. They also reacted more strongly to pain as adults. However, when rats received an injection on postnatal day 14, an age equivalent to adolescence in humans, the patterns of nerve fibers looked like those of normal rats. The researchers surmise that the critical time point responsible for a change in input had passed by day 14, so that the tissue injury and pain did not alter neuronal circuits. The NIDCR study adds pain to the emerging list of early birth stimuli that may have a lifelong impact and suggests that further research is warranted to develop approaches to limit or prevent its effects.

Temporomandibular Disorders (TMD)

The NIDCR is the component of the NIH that has been the primary sponsor for research on TMD, a collection of clinical conditions that produce pain, discomfort, and limited mobility in the temporomandibular joint (TMJ) and associated facial musculature. These disorders are highly complex and still poorly understood. Among the conditions that could potentially produce the pain and dysfunction associated with TMD are primary conditions such as myofacial pain syndromes, and secondary conditions such as osteoarthritis of the TMJ. Other degenerative conditions of this joint, facial trauma, or iatrogenic effects of surgery on or around the TMJ could also play a role. Indeed, it is rapidly being appreciated that painful conditions of the facial masticatory musculature often extend to non-masticatory craniofacial muscles, and may often be part of a more global pain syndrome (fibromyalgia).

NIDCR established the TMD Interagency Working Group (TMDIWG) to facilitate progress in dealing with these disorders through cooperation, communication, and collaboration among agencies that conduct or support TMD-related activities. These activities range from support for biomedical and behavioral research to direct provision of health care services. The TMDIWG provides both a forum for initiating interactions and for tracking their progress. The TMDIWG has also provided a mechanism for the exchange and dissemination of information necessary to maintain effective coordination of DHHS activities related to TMDs.

Activities for FY 2002:

TMD

The TMDIWG has solicited broad input on current NIH and DHHS-related activities, constructed a draft framework around which a short and long-term research agenda addressing the many facets of these disorders can evolve, evaluated the current portfolio of activities and developed implementation plans. Future efforts will include the application of biomimetic principles to develop joint replacements.

Story of Discovery

A dominant theme running through this account of progress and new research initiatives is the role that genes play once scientists have decoded the genetic "words" and translated them into the operational language of the body. One of the most striking gene discoveries of the year has given new meaning to our understanding of one of the body's oldest senses: our ability to taste.

Story of Discovery: Identification and characterization of a family of bitter taste receptors

A father of three, undergoing treatment for heart disease, refuses life-saving medication because of its unbearable bitter taste. A six year old boy is "too full" to eat his cauliflower, but still demands a second helping of chocolate ice cream. On its own, the sense of taste provides animals with information important for survival, from the deliciously sweet-taste of a perfectly ripe peach to the intense bitterness so often associated with toxic or spoiled food. But for us in well-fed 21st century America, the taste for sweetness and salt and the rejection of bitter that remain from our evolutionary past also present major problems. Thus, despite its role (in combination with other senses, most notably smell), in providing the daily pleasure of eating, aspects of human taste also have growing implications in public health. Of all the senses, taste remains the most mysterious; for example, we still do not know how different tastes are detected and discriminated in the oral cavity. However, the human genome project has now helped scientists to start closing this gap in our knowledge.

In the past, progress in understanding taste has been hampered by the very small number of receptor cells. These cells, grouped in taste buds scattered on the surface of the tongue and other regions of the oral cavity, are where taste detection and discrimination takes place. It is believed that taste responses begin when a compound binds to the taste receptors—specific proteins on the surface of these cells. This binding triggers the cells to activate nerves and transmit the information to the brain. In other words, the brain receives information about the pattern of taste cells that are stimulated; and our ability to discriminate between two compounds requires that they stimulate different subsets of taste receptor cells. Thus scientists expect taste receptors to be found on the surface of subsets of taste receptor cells. Last year the first two proteins with these properties were discovered using modern molecular techniques, but it is not yet clear what role they play in taste. Now, using the data generated from the human genome project, a whole family of new receptors has been discovered.

For the last 30 years, it has been appreciated that the ability of mice and humans to detect certain bitter compounds is genetically determined. The approximate positions of several of the genes controlling bitter taste perception have been mapped in mice; and, last year, the position of one was also mapped in humans.

Therefore, scientists searched the growing wealth of DNA sequence information, looking for possible receptor genes in this region of the genome. This search revealed just such a sequence in the right part of the genome and led to the discovery of a whole family of related genes distributed at other sites in the human genome. Intriguingly, when the corresponding receptor genes from mice were mapped, many corresponded with bitter taste loci. Additional circumstantial evidence suggested that these might be taste receptors. For example, as expected, they are selectively expressed in the membranes of subsets of taste receptor cells. But what really sets this discovery apart from the earlier investigation is the proof that at least some members of the new gene family actually function as taste receptors—that is, they trigger cellular activity after binding to bitter compounds.

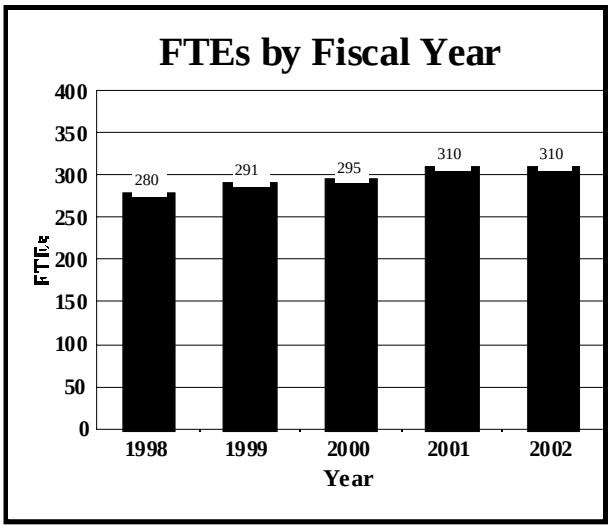
In biology, bitter taste appears to be an almost uniform warning of toxicity. Indeed many different, naturally occurring, poisonous compounds taste bitter to humans and are aversive stimuli for laboratory animals. However, structurally these molecules have little or no similarity and so it has never been clear why they should all taste bitter. What do these new receptors tell us about how bitter taste works? It turns out that each receptor cell that contains one receptor actually carries the entire family of these receptors on its surface. Therefore, the pattern of cells stimulated by a bitter tasting compound that binds to one of these receptors is indistinguishable from the pattern produced by a different bitter tasting compound binding to a different receptor. Since the brain receives and interprets information about the patterns of cells that are activated, this provides a logical explanation for the uniform bitter taste of toxins.

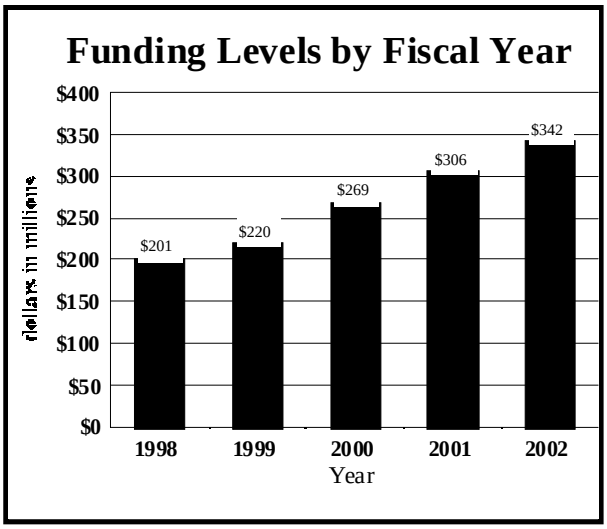
These findings may lead to advances in our knowledge about the organization of the nervous system and its responses to the environment. Identification of functionally defined taste receptors provides molecular tools to mark specific taste receptor cells, define signaling pathways, dissect receptor specificity, generate topographic maps, and trace the neuronal connectivity circuits. A deeper understanding of taste mechanisms could also translate into improved therapeutic regimes. Researchers have found that certain drugs for AIDS, heart disease, and depression taste so bad or so ruin the flavors of food that patients abandon life- saving medications. The ability to block the bitter taste receptor could dramatically improve compliance with life-saving drugs. Moreover, researchers have also shown that the sense of taste is linked to a predisposition toward dietary choices that may contribute to obesity and health related problems including increased risk of diabetes, heart disease, and stroke. Variations between bitter taste receptors within the human population may provide a valuable tool for predicting the likely dietary choice of individuals, and their likelihood for developing certain diseases.

Budget Policy

The FY 2002 budget request for the NIDCR is $341,898,000, including AIDS, an increase of $35,687,000 and 11.7 percent over the FY 2001 level, $72,994,000 and 27.1 percent over FY 2000.

A five year history of FTEs and funding levels for NIDCR is shown in the graphs on the next page:





One of NIH's highest priorities is the funding of medical research through research project grants (RPGs). Support for RPGs allows NIH to sustain the scientific momentum of investigator-initiated research while providing new research opportunities. The FY 2002 request provides average cost increases for competing RPGs equal to the Biomedical Research and Development Price Index, estimated at 4.3 percent. Noncompeting RPGs will receive increases of 3 percent on average for recurring direct costs. In FY 2002, total RPGs funded will be 679 awards, an increase of 29 awards over the FY 2001 estimate, the highest annual total ever awarded.

Promises for advancement in medical research are dependent on a continuing supply of new investigators with new ideas. In the FY 2002 request, NIDCR will support 325 pre- and postdoctoral trainees in full-time training positions. An increase of 10 percent over FY 2001 levels is provided for stipends and training-related expenses (e.g., health insurance, research supplies and equipment, and travel to scientific meetings).

The FY 2002 request includes funding for 16 research centers, 115 other research grants, and 29 R&D contracts. The R&D contracts mechanism also includes support for 3 contracts for the Extramural Clinical and Pediatric Loan Repayment Programs.

The Research Management and Support (RMS) budget activity has increased 11.5 percent over the FY 2001 level. The RMS activity is used to sustain, guide, and monitor both the extramural and intramural activities of the Institute. The activities that will be bolstered include overall

scientific program direction and administration, as well as health promotion and information dissemination programs, technology transfer activities, and support of central NIH services.

The mechanism distribution by percent change and dollars is displayed in the graphs on the next page: